Complete Summary

GUIDELINE TITLE

Genital herpes. In: Sexually transmitted infections: UK national screening and testing guidelines.

BIBLIOGRAPHIC SOURCE(S)

Geretti AM. Genital herpes. In: Ross J, Ison C, Carder C, Lewis D, Mercey D, Young H. Sexually transmitted infections: UK national screening and testing guidelines. London (UK): British Association for Sexual Health and HIV (BASHH); 2006 Aug. p. 76-84. [60 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Genital herpes (GH) (herpes simplex-1 and herpes simplex-2 infection)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Risk Assessment
Screening

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Urology

INTENDED USERS

Advanced Practice Nurses
Clinical Laboratory Personnel
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide advice on what tests for genital herpes (GH) are most appropriate in a United Kingdom (UK) genitourinary (GU) clinic setting (excluding human immunodeficiency virus [HIV]-infected patients)
- To provide a basis for audit
- To support clinics when bidding for additional resources to meet national standards

TARGET POPULATION

Individuals in the United Kingdom at risk for genital herpes

INTERVENTIONS AND PRACTICES CONSIDERED

1. Screening of asymptomatic patients (not recommended)
2. Serologic testing for herpes simplex virus (HSV) type 1 and 2 antibodies
3. Western blot diagnosis of glycoproteins G1 and G2
4. Enzyme-linked immunosorbent assays (ELISAs)
5. Cultures for antiviral sensitivity testing
6. Real-time polymerase chain reaction (PCR) for HSV DNA testing
7. Direct immunofluorescence assay (IFA) or enzyme immunoassay (EIA) detection of viral antigen
8. Site of testing (lesion swabs or scrapings, blood, Tzanck or Papanicolaou smear)
9. Screening of pregnant women
10. Frequency of testing
11. Follow-up testing for cure (not recommended)

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of test methods
- Positive predictive value of herpes simplex virus (HSV) type-specific assays

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MeSH: "Herpes-genitalis-diagnosis," "Herpes-simplex-diagnosis," "Sensitivity," "Specificity" (1983 to April 2004). Further evidence was obtained from the International Herpes Management Forum guidelines and the 2002 Center for Disease Control and Prevention (CDC) Sexually Transmitted Infections (STI) treatment guidelines.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

Ib: Evidence obtained from at least one randomised controlled trial

IIa: Evidence obtained from at least one well designed controlled study without randomisation

IIb: Evidence obtained from at least one other type of well designed quasi-experimental study

III: Evidence obtained from well designed non-experimental descriptive studies

IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guidelines have been developed following the methodological framework of the Appraisal of Guidelines Research and Evaluation instrument (AGREE - adapted as described in *Int J STD and AIDS* 2004 15:297-305).

The extent to which the guideline represents the views of intended users has been addressed primarily by the authorship coming from the multidisciplinary membership of the Bacterial Special Interest Group (BSIG). As practising clinicians the authors were able to draw on their experience of applying the tests to symptomatic and asymptomatic patients, but it was not feasible to obtain formal input from representative patients.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After drafting, other health care professionals and professional bodies in genitourinary (GU) medicine were asked to comment, the draft guidelines posted on the British Association for Sexual Health and HIV (BASHH) website for 3 months, and all comments reviewed before final publication.

Prior to submission this guideline was distributed to all members of The Herpes Simplex Advisory Panel. Their comments were noted and incorporated into the current document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the level of evidence (**I-IV**) and grade of recommendation (**A-C**) are provided at the end of the "Major Recommendations" field.

Recommended Tests

Screening of asymptomatic genitourinary (GU) clinic attendees by either herpes simplex virus (HSV) antibody testing (**Evidence Level IV; Grade of Recommendation C**) or HSV detection in genital specimens (**Evidence Level IIa; Grade of Recommendation B**) is not recommended at present, although this area is under active review.

HSV Antibody Testing

- Testing for HSV type-specific antibodies can be used to diagnose HSV infection in asymptomatic persons.
- HSV-2 antibodies are indicative of genital herpes (GH). HSV-1 antibodies do not differentiate between genital and oropharyngeal infection.
- Arguments in favour of serological screening include:
    a. HSV-2 infection rates are as high as or higher than those of other sexually transmitted infections (STIs) for which screening is in place.
    b. Persons with asymptomatic or undiagnosed infection may transmit HSV to sexual partners or neonates.
    c. Behavioural changes, condom use and suppressive antiviral therapy reduce the risk of HSV transmission.
    d. Vaccines may soon become available to protect HSV seronegative persons from infection and disease.
    e. HSV-2 seropositive persons who engage in high-risk sexual behaviour can be counselled about the increased risk of HIV acquisition (**Evidence Level Ia, Grade of Recommendation A**).
- Arguments against screening include:

    a. The specificity and sensitivity of current antibody assays are <100%.
    b. False-positive results generate unnecessary psychological morbidity.
    c. False-positive and false-negative results lead to inappropriate counselling.
    d. Counselling of HSV-2 seronegative HSV-1 seropositive persons is problematic, given the large proportion of GH due to HSV-1.
- Assays should be used that detect antibodies against the antigenically unique glycoproteins gG1 and gG2 (**Evidence Level III, Grade of Recommendation B**).
    - Western blot (WB) is the diagnostic gold-standard. It is >97% sensitive and >98% specific, but is labour-intensive and not commercially available.
    - Several commercial assays have become available. (Well validated in-house assays have also been developed.) Among commercial assays, the HerpeSelect-1 and HerpeSelect-2 enzyme-linked immunosorbent assay (ELISA) immunoglobulin G (IgG), and HerpeSelect 1 and 2

Immunoblot IgG (Focus Technology, California, US) have been approved by the American Food and Drug Administration. In sexually active adults, sensitivity and specificity of ELISA relative to WB are 91% and 92% for HSV-1 and 96% and 97% for HSV-2. Immunoblot sensitivity and specificity are 99% and 95% for HSV-1 and 97% and 98% for HSV-2 (http://www.herpeselect.com/).

- HSV seroprevalence rates in the local population and the presence or absence of risk factors for GH influence the positive predictive value of HSV type-specific antibody assays. Local epidemiological data and patient demographic characteristics should guide testing and result interpretation (**Evidence Level III, Grade of Recommendation B**).
- In patients with a low likelihood of GH, a positive HSV-2 result should be confirmed in a repeat sample or by using a different assay (**Evidence Level III, Grade of Recommendation B**).
- Type-specific antibody can take months to develop and false-negative results may occur early after infection. In first episode disease the diagnostic use of type-specific antibody testing will require follow-up samples after 3 months to demonstrate seroconversion.

Direct Detection of HSV in Genital Lesions

- Methods should be used that directly demonstrate HSV in swabs or scrapings from a lesion (**Evidence Level Ia, Grade of Recommendation A**).
- Cytological examination (Tzanck and Papanicolaou smears) has modest diagnostic specificity and sensitivity and should not be relied upon for diagnosis (**Evidence Level Ib, Grade of Recommendation A**).
- HSV isolation in cell culture is the diagnostic gold standard and the current routine diagnostic method in the United Kingdom (UK). Isolates can be typed and tested for antiviral susceptibility. Virus culture is slow, labour-intensive and expensive. Specificity is virtually 100%, but levels of virus shedding, quality of specimens, and transport conditions influence sensitivity. First-episode ulcers more often yield the virus than recurrent lesions (82% versus 43%). Average sensitivity is 52% to 93% for vesicles, 41% to 72% for ulcers and 19% to 27% for crusted lesions. Delayed sample processing and lack of specimen refrigeration after collection and during transport significantly reduce the yield of virus culture.
- HSV deoxyribonucleic acid (DNA) detection by polymerase chain reaction (PCR) increases HSV detection rates by 11 to 71% compared with virus culture. HSV PCR is widely available in UK virology laboratories for testing of cerebrospinal fluid in patients with neurological disease. There have been at least 14 large studies comparing virus culture with PCR for the detection of HSV in muco-cutaneous swabs, together comprising data from over 3,500 patients. These studies demonstrated that the relative sensitivity of virus culture averaged 70% and ranged between 25% and 89%. PCR should be implemented, after local validation, as the preferred diagnostic method for GH (**Evidence Level Ib, Grade of Recommendation A**).
- Unlike virus culture, PCR-based methods do not rely on virus growth and may allow less stringent conditions for sample storage and transport.
- Real-time PCR assays allow detection and typing of HSV in a single reaction tube, with faster turn-around-times (potentially 2 hours) and lower risk of contamination than traditional PCR assays. The RealArt™ HSV 1/2 PCR kit (Artus, Germany) is commercially available for use in real-time assays.

- Viral antigen can be detected by direct immunofluorescence assay (IFA) using fluorescein-labelled monoclonal antibodies on smears, or by enzyme immunoassay (EIA) on swabs.
- IFA shows lower sensitivity (74%) and specificity (85%) than virus culture and cannot be recommended (**Evidence Level Ia, Grade of Recommendation A**).
- Commercially available EIAs (e.g., HerpChek, PerkinElmer, Belgium) show ≥ 95% specificity and 62% to 100% sensitivity relative to virus culture. Sensitivity may be higher than virus culture for typical presentations and late specimens, but lower for cervical or urethral swabs and recurrent episodes. HerpChek does not differentiate between HSV types.

Recommended Sites for Testing

- Clotted blood (if serology indicated)
- Lesion material (if lesion is present)

Factors Which Alter Tests Recommended or Sites Tested

- Genital lesions that could be due to HSV (direct detection)
- Serological screening should be considered in persons with a history of recurrent genital symptoms of unknown aetiology when direct virus detection methods (e.g., virus culture or PCR testing of genital specimens) have been repeatedly negative (**Evidence Level III, Grade of Recommendation B**).
- Patients who are known contacts: serological screening should be considered for sexual partners of persons with GH, where there is a concern about transmission. Some couples may find that their HSV status is concordant. Discordant couples can identify strategies to prevent transmission (**Evidence Level III, Grade of Recommendation B**).

Risk Groups

- Gay men: no alteration to standard recommendation
- Sex workers: no alteration to standard recommendation
- Young patients: HSV-2 antibody tests should not be used in children <14 years of age due to a high false-positive rate (**Evidence Level III, Grade of Recommendation B**).

Other

- Pregnant women: Routine screening of pregnant women, and their partners, to identify those already infected and those at risk of infection remains controversial. The identification of serologically discordant couples may offer the opportunity to counsel seronegative women about strategies to prevent infection during pregnancy (**Evidence Level III, Grade of Recommendation B**). Screening of pregnant women is recommended where there is a history of genital herpes in the partner (**Evidence Level III, Grade of Recommendation B**).
- Women with a history of hysterectomy: no alteration to standard recommendation

Recommendation for Frequency of Repeat Testing

- In HSV-2 seropositive persons with a low likelihood of infection, a positive HSV-2 result should be confirmed in a repeat sample or by using a different assay.
- Repeat testing of HSV seronegative women with seropositive male partners may be helpful in pregnancy.
- Decision about repeat testing should be guided by the patient's history of potential exposure.
- In patients with a suspected recent infection who test HSV antibody negative early after presentation, repeat serological testing is recommended after three months as seroconversion may be delayed.
- Repeat direct testing for HSV in genital specimens is not indicated in the presence of typical recurrent HSV lesions as long as viral detection and typing were successfully accomplished during a previous episode.

Recommendation for a Test of Cure

Not recommended

Definitions:

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomised controlled trials

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IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A. Evidence at level Ia or Ib
B. Evidence at level IIa, IIb, or III
C. Evidence at level IV

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate screening and diagnosis of herpes simplex virus infection

POTENTIAL HARMS

- False-positive test results generate unnecessary psychological morbidity.
- False-positive and false-negative test results lead to inappropriate counselling.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Herpes simplex virus (HSV) type-specific antibody assays may not be available in all laboratories.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Aug

GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

No specific or external funding was sought or provided in the development of this guideline.

GUIDELINE COMMITTEE

Screening Guidelines Steering Committee
Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Anna Maria Geretti, Dept of Virology, Royal Free Hospital, London

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Herpes Simplex Advisory Panel is a special interest group of the Medical Society for the Study of Venereal Diseases (MSSVD), currently sponsored by an educational grant from GlaxoSmithKline. Members have undertaken research and been funded to attend meetings by GlaxoSmithKline.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from British Association for Sexual Health and HIV Web Site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Specifications for the development of UK guidelines on the management of sexually transmitted infections (STIs) and closely related conditions 2005. London (UK): British Association of Sexual Health and HIV (BASHH); 2005. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the British Association for Sexual Health and HIV Web site.

Additionally, auditable outcome measures can be found in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on June 25, 2008. The information was verified by the guideline developer on October 20, 2008.

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